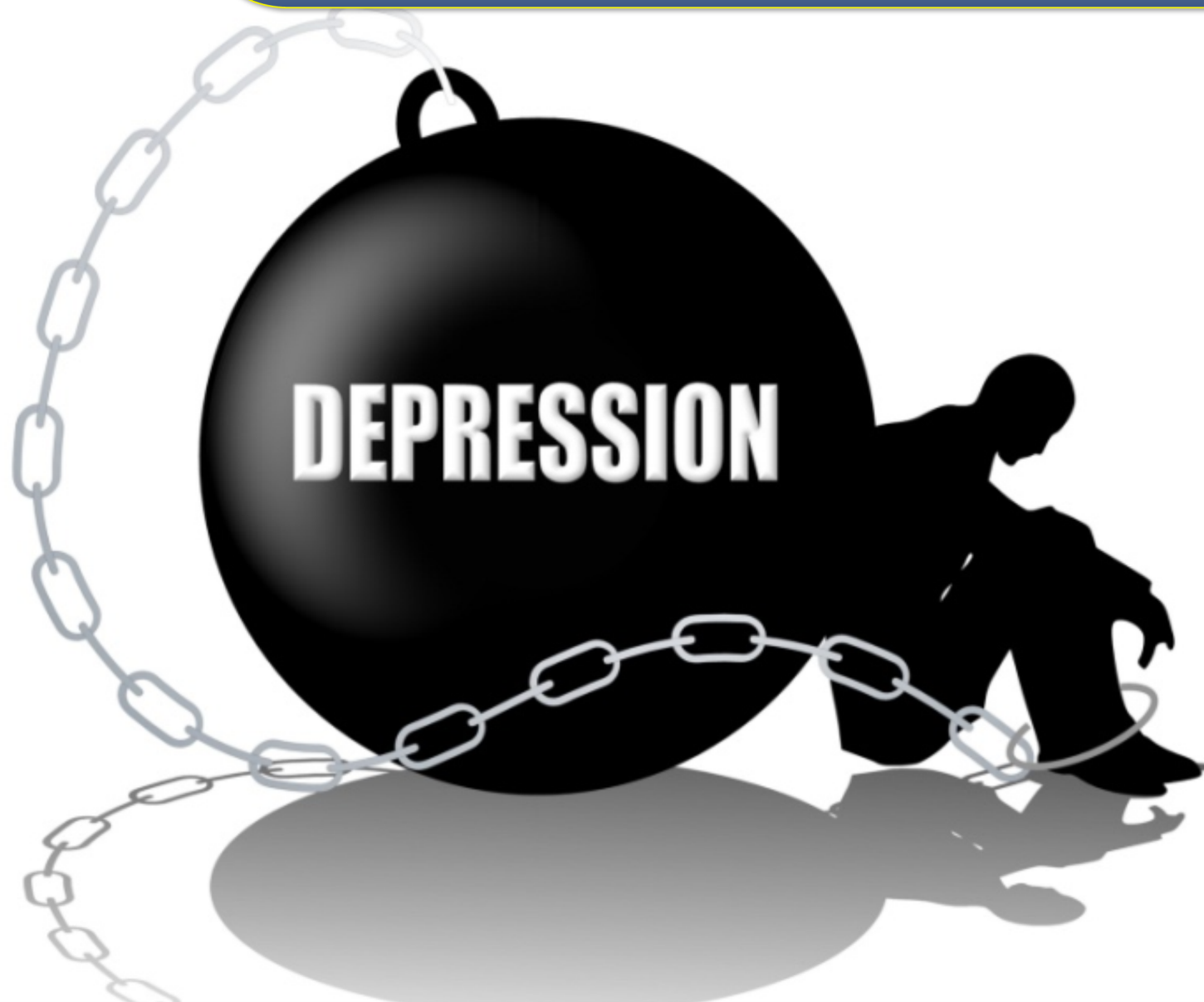


Draw **Pharmacology** *in your mind*



If you are a pharmacy student
If you are postgraduate and want
to revise pharmacology by an
easy way
If you are using any pharmacology
reference
this file will aid you

> **And wait for more** <

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لا تتسولوني من صالح دعائكم

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د. آلاء نصر

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Ph. Alaa Nasr

Depression

Types

Unipolar depression
(Reactive depression)

Bipolar depression (Manic-depressive illness)

Definition / Case

Condition in which the patient swings between **normal** mood and **depression**

Condition in which the patient swings between **mania** and **depression**

Cause

Stressful life events and conditions

Hereditary, appears in *early adult life*

Symptoms

1. Emotional symptoms

- Intense feeling of sadness
- Pessimism تشاؤم
- Guilt احساس بالذنب
- low self-esteem عدم تقدير النفس
- Despair يأس
- Inability to feel pleasure
- Suicidal attempts

2. Biological symptoms

- Decreased physical activities
- Retardation of thought
- Loss of appetite and weight
- Sleep disturbances
- Loss of libido (sexual desire)

3. Manic symptoms !!

- Excessive enthusiasm حماس زائد
- Mental alertness
- Increased self-confidence
- Hyperactivity
- Rapid thought and speech
- Irritability
- Impatience and aggression

Etiology

Monoamine theory

Monoamine theory was introduced after noticing that **Reserpine** (*a drug used for treatment of hypertension, can pass BBB*) depleting the brain stores of monoamines (NA, 5HT, DA .. etc) → **leading to depression !!**

Scientists thought that depression is caused by **deficiency of monoamines** in certain areas of the brain .. **reason 1**

They found that antidepressant drugs can't show their desired effect except after **2-3 weeks** at least while scientists are sure that those drugs increase monoamines in the brain from day 1 in the treatment !!

But later, studies did not support this simple form of theory.. **How !**

So again scientists thought that there should be **another cause** for depression besides the first 1 !!

Monoamines involved in depression are

1. ↓ **NA** → responsible for **biological symptoms**
 2. ↓ **5HT** → responsible for **emotional symptoms**
- Manic symptoms** are caused by ↑ **level of monoamines !!**

So, causes of depression are

1. Autoreceptor hyper-responsiveness
2. Decrease monoamines in the synapse

From this we can conclude that **reason number 2** for depression is the **Adaptive changes in the autoreceptors** (*autoreceptor hyper-responsiveness*)

Lets take it step by step ..

First.. "Autoreceptors" are presynaptic receptors work as *regulators / inhibitors* for the release of the neurotransmitter from its nerve ending

Second.. most receptors of the body undergo "up-regulation" (↑ in number) or "down-regulation" (↓ in number) *according to the amount of the neurotransmitter in the synapse* **How !**

- ♦ If the neurotransmitter level ↑ → down-regulation
- ♦ If the neurotransmitter level ↓ → up-regulation

Third.. If monoamines level in synapse ↓ (*in case of depression*) → upregulation of autoreceptors → more decrease in their levels !

Examples

Clomipramine
Desipramine
Imipramine
Amitriptyline
Nortriptyline
Doxepin
Maprotiline



Pharmacological actions

1. ↑ NA → mental alertness & physical activity
2. ↑ 5HT → mood elevation
3. No effect on normal persons

Mechanism

1. ↓ neuronal reuptake of NA and 5HT
2. After the blockade occur → immediate ↑ in synaptic concentration of NA and 5HT (**1st effect**)
3. 2-3 weeks the ↑ in the synaptic concentration of NA and 5HT leads to adaptive changes (down-regulation of presynaptic autoreceptors) (**2nd effect**) → ↑ firing of neurons

Pharmacokinetics

1. **Absorption** → TCAs are lipophilic (3rd amines), well absorbed from GIT, can cross BBB
2. **Distribution** → strongly bound to plasma proteins so, **contraindicated** with other drugs which bind strongly to plasma proteins (ex. warfarin)
3. **Metabolism** → metabolized in liver
 - Phase I gives an **active** metabolite → **long half-life** ex. Amitriptyline → Nortriptyline
 - Phase II gives an **inactive** metabolite
4. **Excretion** → excreted in urine as inactive glucuronides it may take several days (10-80 hrs)

Side effects

1. **Cardiac arrhythmias** (the ↓ monoamine uptake → ↑ catecholamine activity + they bind to Na⁺ channels in cardiac membrane)
2. **Antimuscarinic action** = Dry mouth + Blurred vision + Constipation + Glaucoma + Urine retention
3. **α-blockade effect** = postural hypotension
4. **Antihistaminic action** = sedation + drowsiness
5. **Delayed ejaculation** (so, it can be used for males having premature ejaculation but it is not preferred for its side effects)

First.. what is the goal of treatment ?

1. ↑ monoamine level in the synaptic cleft (primary / acute effect)
2. Down-regulation of the presynaptic autoreceptors

How !

Antidepressants → ↑ monoamine level in the synaptic cleft (*primary effect*) → adaptive changes (2-3 weeks) → down-regulation of autoreceptors → ↑ firing rate of neurons (*secondary effect*)

Antidepressants

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TCAs Tricyclic antidepressants

Indications

1. All forms of depression
2. Anxiety disorder (manic disorders, phobic disorders, OCD)
3. Certain sleep disorders
4. Chronic pain syndrome due to (its mood elevating effect + analgesic activity)
5. Depression associated with schizophrenia

Contraindications of TCAs

TCAs are contraindicated in **manic depressive illness** alone as they tend to switch the depressed patient to the manic phase so they should be administered with mood stabilizing drug ex. **Li salts**

Over-dosage (suicidal attempts)

Symptoms: cardiac arrhythmias + ventricular fibrillation + convulsions + exaggeration of antimuscarinic effects
Treatment: IV administration of NaHCO₃

- ◆ ↑ the ratio of non-ionized TCA to ionized TCA
- ◆ ↓ the binding of TCA to Na⁺ channels in the cardiac membrane

Drug-Drug interaction

1. TCAs (↑ monoamines) + **MAOIs** (↓ their degradation) = hypertensive crisis
2. TCAs (strongly bound to plasma proteins) + **Aspirin or Phenylbutazone** = compete on plasma proteins = toxicity
3. TCAs are metabolized by liver microsomal enzymes so their action can be :
 - ◆ Reduced by LME inducers ex. **Barbiturates , Rifampicin**
 - ◆ Increased by LME inhibitors ex. **SSRIs, Proton pump inhibitors, Ketoconazole, Oral contraceptives, Antipsychotics**

Examples

Fluoxetine
Paroxetine
Fluvoxamine
Citalopram
Escitalopram
Sertraline



SSRIs Selective Serotonin Reuptake Inhibitors

- A newer group of antidepressants
- They can specifically inhibit the reuptake of serotonin
- They are now the *most widely used drugs* for treatment of depression and anxiety disorders

Mechanism

The same as TCAs but more selective to 5HT

Advantages of SSRIs over TCAs

1. Equally effective to TCAs
2. Less side effects and less sedation
3. Safer in case of over dose

Pharmacokinetics

1. Well absorbed from GIT
2. Metabolized by Cyt. P₄₅₀
3. **Fluoxetine** has longer half-life than other drugs in this class as it is metabolized to an active metabolite

Side effects

1. Nausea
2. Insomnia
3. **Sexual dysfunction (on prolonged use)**

Drug-Drug interaction

1. SSRIs are strong LME inhibitors → so, not used with **TCAs** or any drug with a narrow therapeutic index → ↓ metabolism → toxicity
2. Not used with **MAOIs** this would lead to **serotonin syndrome** (a life-threatening condition characterized by tremors, hyperthermia, cardio-vascular collapse and **death** !!) so for safety **wash out period of 6 weeks is required** before administration of one of them after the other.

Types of MAO enzyme

♦ MAO-A

- Metabolizes NA, 5HT, DA and Tyramine
- Found in higher concentration in the gut and peripheral tissues
- Its inhibition is responsible for the antidepressant effect of MAOIs

♦ MAO-B

- Acts mainly at dopamine

Classification of MAOIs

♦ 1st generation MAOIs

- They are **irreversible** inhibitors of both MAO-A and MAO-B

Example → Phenelzine - Tranylcypromine

♦ 2nd generation MAOIs

- Selective **reversible** inhibition of MAO-A

Example → Moclobemide

In both generations the 1st effect will happen ($\uparrow$ level of monoamine in the synaptic cleft) then the 2nd effect occurs (adaptive changes and down-regulation of autoreceptors) and this $\uparrow$ firing of serotonergic neurons

Drug-Drug Drug-Food interaction

1. **Ephedrine and Amphetamine** (indirectly acting sympathomimetic)

$\uparrow$ monoamines → **hypertensive crisis**

2. **TCAs**

$\uparrow$ monoamines → **hypertensive crisis**

3. **Levodopa**

Precursor for DA & NA → **hypertensive crisis**

4. **SSRIs**

$\uparrow$ serotonin → **serotonin syndrome**

5. **Tyramine**

- Indirectly acting sympathomimetic amine

- Found in some food like Cheese, Yogurt, Yeast extract → **hypertensive crisis** called "**Cheese effect**"

Antidepressants

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MAOIs Monoamine Oxidase inhibitors

Others

Examples

Mirtazapine - Trazodone - Venlafaxine - Buprobion



Mechanism

- Antagonists at presynaptic receptors the → $\uparrow$ release of monoamines

- *They have less side effects and less drug interactions*

Li salts (mood stabilizing drugs)



Used to control mood in bipolar depression (decrease NA & 5HT)

Mechanism

- They decrease the formation of IP₃ (inositol triphosphate) the 2nd messenger involved in normal neuronal signal transduction → nerve firing will $\downarrow$ "calming effect"

Pharmacological action

Calming effect but it requires several days to weeks for the effect to be achieved

Pharmacokinetics

They have a **very narrow therapeutic index** so, should be carefully monitored

Toxicity symptoms

Nausea - Thirst - Polyuria - Tremors - Confusion

ECT Electroconvulsive therapy

- Used to control severe (suicidal or resistant) forms of depression.

- It involves stimulation through **electrodes in both sides of the head**.

- It increase the CNS response to NA and 5HT

Precautions before application

1. The patient is slightly anesthetized
2. The patient is paralyzed by a neuromuscular blocker to avoid physical injury

Disadvantages

Memory loss, confusion for days or weeks

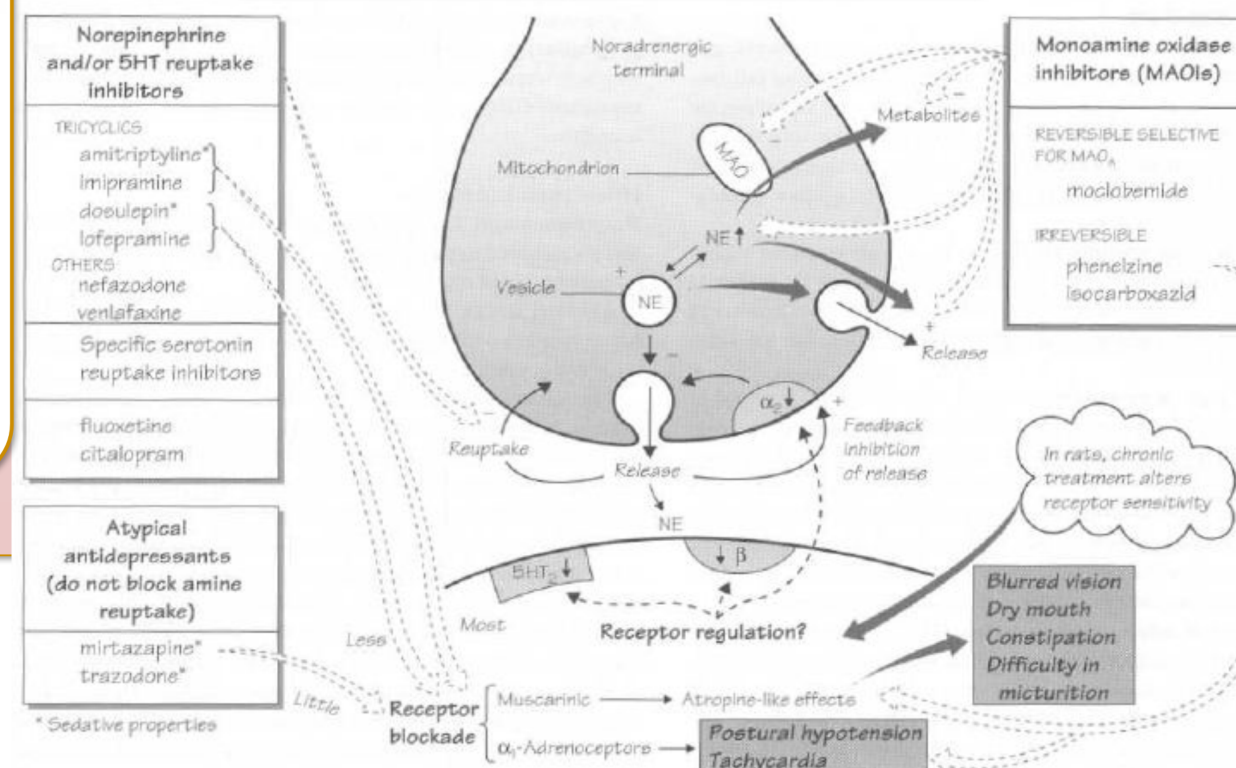


Figure illustrating antidepressants mechanisms from "Medical pharmacology at a glance"